Clinical review

West Nile encephalitis

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Although West Nile encephalitis is yet to spread to the United Kingdom, it is becoming more prevalent in the rest of the world. This article reviews the recent outbreaks and examines the current methods of diagnosis, treatment, and prevention

In the summer of 1999, crows dropping from the New York sky, sick birds at the Bronx zoo, and an unusual cluster of cases of human encephalitis heralded the arrival of West Nile virus in North America.[1] Although there were only 62 cases and seven deaths in 1999, the virus has since moved across the continent, and during 2002 there were more than 3500 cases and 200 deaths (see fig A on bmj.com). West Nile virus also occurs in Africa, parts of Asia, and southern Europe, with recent outbreaks in Romania, Russia, and Israel (fig 1).[2–4] Unpublished evidence is reported to show that birds in the British Isles may also have antibody to the virus.[5] The recent outbreaks of West Nile virus have drawn attention to the devastating potential of mosquito-borne neurogenic flaviviruses to spread (see box 1 for details).[6]

We reviewed the epidemiology and clinical features of infection with West Nile virus, highlighting the many unanswered questions about how and why such viruses spread and focusing on how to recognise, diagnose, and treat patients with the infection.

Summary points

- West Nile encephalitis is caused by West Nile virus, an arthropod-borne virus which is spreading
- During 2002 the virus caused more than 3500 cases and 200 deaths in the United States
- The virus occurs in Africa, the Middle East, parts of Asia and Australia, and southern Europe, but its presence in Britain has not yet been confirmed
- Elderly people and those on immunosuppressive drugs are at special risk
- There is no antiviral treatment or vaccine, and attempts to halt the disease with mosquito control have had only limited success

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Sources and selection criteria

We examined new information from recent outbreaks in America, Israel, and Southern Europe cited on PubMed and the internet to 11 December 2002. We also examined literature on West Nile virus from before 1966.

Historical perspective

In 1937 British virologists first isolated West Nile virus from the blood of a febrile woman in the West Nile region of northern Uganda. It was soon shown to be transmitted between vertebrate hosts (especially birds) by mosquitoes, thus conforming to the ecological description "arthropod-borne virus" or arbovirus. Although not associated with neurological disease at that time, it was shown by serological cross reactivity to be closely related to two recently identified neurotropic viruses: Japanese encephalitis virus and St Louis encephalitis virus. Sporadic cases and larger outbreaks of febrile disease (West Nile fever) were reported in Africa, the Middle East, and Asia (table).[11] Although meningeal irritation was noted, the first cases of encephalitis due to West Nile virus were, ironically, in New York in the early 1950s when the virus was given as an experimental (and unsuccessful) treatment for advanced cancer. The first naturally occurring cases of West Nile encephalitis were in the elderly residents of a nursing home in Israel.[12] Outbreaks of equine and human meningoencephalitis occurred in southern France during the 1960s, and a subtype of West Nile

P+ *A map of US distribution and spread can be found on bmj.com*

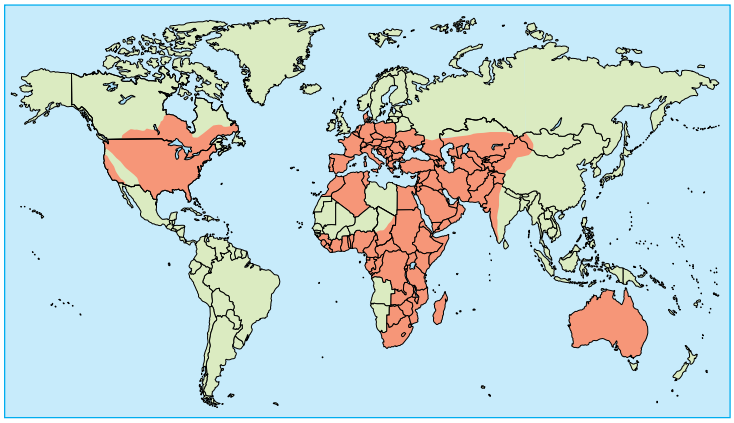

Fig 1 Approximate global distribution of West Nile virus (or its subtype, Kunjin virus)

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Box 1: Related viruses

Japanese encephalitis virus
Numerically this is the most important of the neurogenic flavivirus, with an estimated 35-50 000 cases and 10 000 deaths annually.[7] The virus is found in South East Asia, China, the Pacific Rim, and India, and is spreading with recent cases in northern Australia and Nepal. It is transmitted by *Culex tritaeniorhynchus* mosquitoes, which breed in rice paddies. Most people are infected during childhood, but only a few (about 1 in 150) develop fever, and even fewer develop central nervous system disease. In endemic areas most cases of encephalitis occur in children, but travellers are at also risk. Clinically the virus causes a severe meningoencephalomyelitis, often associated with extrapyramidal movement disorders; it can also present as meningitis or occasionally a polio-like flaccid paralysis. Seizures and raised intracranial pressure are common in children. There is no antiviral treatment. A formalin inactivated vaccine (too expensive for most residents of endemic areas) is recommended for travellers, though occasionally it causes side effects.[8]

St Louis encephalitis virus
First identified in the 1930s after encephalitis outbreaks around St Louis, Missouri, this virus was, until recently, the most important flavivirus in the United States. The virus occurs naturally in many birds and is transmitted by *Culex* mosquitoes. Sporadic cases occur every year, particularly in the southern states,[9] but in 1990 there were more than 200 cases, and in 1975 there was a major outbreak, with 3000 cases.

Murray Valley encephalitis virus
This Australian flavivirus cousin causes sporadic cases of encephalitis most years in the north and west of Australia and in New Guinea, with occasional small outbreaks (up to 20 cases).[10] The virus is transmitted between wild birds by *Culex* mosquitoes.

Box 2: West Nile encephalitis–key unanswered questions

- Ecology—How and why does West Nile virus spread? Will it continue to cause large outbreaks in North America? Where else might it reach?
- Clinical epidemiology—Why has the clinical pattern changed, and what are the roles of viral, host, and other factors in determining the clinical presentation?
- Treatment—What are the prospects for antiviral therapy?
- Prevention—How can outbreaks be predicted and stopped? What role will vaccines have in the future?

virus (Kunjin virus) was isolated in Australasia. Since the 1990s the clinical epidemiology of West Nile virus seems to have changed, with increasing frequency and severity of outbreaks, including urban disease (table).[2–4 13]

West Nile virus

The virus is a member of the Japanese encephalitis serogroup of the genus *Flavivirus*, family Flaviviridae. The flaviviruses are thought to have evolved from a common ancestor as recently as 10 000 years ago and are rapidly evolving to fill new ecological niches.[14] Like other flaviviruses, West Nile virus is a small, single stranded, positive sense RNA virus comprising about 11 000 nucleotides wrapped in a nucleocapsid and surrounded by a lipid membrane. An envelope glycoprotein on the surface is thought to be responsible for mediating viral entry into cells, tissue tropism, and host range.

Molecular phylogenetic studies have shown that isolates of the virus can be divided into two lineages. Linage II strains have mostly been found in Africa, whereas lineage I strains are more widely distributed and have been responsible for all the recent large outbreaks. This has led to the suggestion that they may be more virulent, though neuroinvasive strains have been shown in both lineages in animal models.[15]

Ecology

In nature West Nile virus is transmitted between birds by mosquitoes. Recent studies in the United States have found infection in 146 species of bird and 29 species of mosquito. Members of the order Passeriformes (jays, blackbirds, finches, warblers, sparrows, crows) seem to be important in maintaining the virus in nature (because of their high viraemias). Members of the Corvidae family (crows, blue jays) are particularly susceptible. Because of their low and brief viraemias, humans and horses do not normally transmit the virus to biting mosquitoes and are thus considered dead end hosts. Of the many mosquito species from which West Nile virus has been isolated, *Culex* species, particularly *C pipiens*, seem to be important in the enzootic cycle, though different species may act as "bridging vectors," transmitting the virus to humans (fig 2).

Details of selected outbreaks of West Nile virus infection. Criteria for admission to hospital, case definitions, and diagnostic methods varied between outbreaks, and some numbers are approximations

Country and year of outbreak	No of suspected cases	No of cases investigated	Confirmed cases	Deaths	Note
Israel, 1957[12]	419	247	c180	4	Included first naturally occurring encephalitis cases (12 patients)
South Africa, 1974[11]	18 000	558	307	0	Estimated 18 000 cases of West Nile fever
Camargue, France, 1962-6			14	1	Many horses also affected
Algeria, 1994	50	18	17	8	
Romania, 1996[3]	835	509	393	17	Continuing cases in 1997-9
Tunisia, 1997	173	129	111	8	
Congo, 1998	35	35	23	0	Military personnel newly arrived in this area
New York, USA, 1999[23]	719	719	62	7	
Volograd region, Russia, 1999[4]	826	318	183	40	
Israel, 2002[2]			233	33	91 cases with no hospital admission also identified
USA, 2000-1			85	24	
USA, 2002			3829	225	Largest outbreak of encephalitis

How the virus is introduced to new areas is not completely understood. Migratory birds are thought to be important for the movement of the virus from Africa into southern Europe. They may have been involved in the virus's introduction into North America, though imported exotic birds, a viraemic human, or inadvertently transported mosquitoes seem more likely.[16] Evidence from studies in molecular genetics suggests there was a single introduction into the United States of a strain closely related to one isolated from a goose in Israel.[17] A complex interplay of viral, avian, mosquito, human, and climatic factors may contribute to the large outbreaks that have characterised the disease in recent years. During the 2002 outbreak in the United States it became clear that transmission can also occur via transplanted organs, infected blood products, and possibly breast milk.[18]

Clinical epidemiology

Most human infections with West Nile virus are asymptomatic. Epidemiological surveys after the 1999 outbreak in New York showed that about one in five people infected with the virus develops West Nile fever, and only about one in 150 develops central nervous system disease.[13] These are similar to the rates seen in the outbreak in Romania in 1997[3] but are much higher than those reported in Egypt and South Africa.[11 19] In New York, Romania, and Israel the risk of febrile disease and neurological disease increased with age, which may in part explain the differences compared with parts of Africa. In Egypt most people are infected during childhood, and neurological disease is rare.[19] But in South Africa a large outbreak affected an estimated 18 000 people of all ages, yet only one case of encephalitis was reported.[11]

Clinical features

After an incubation period, which is typically 2-6 days but may extend to 14 days, patients with West Nile fever develop a sudden onset of an acute non-specific flu-like illness, characterised by high fever with chills, malaise, headache, backache, arthralgia, myalgia, and retro-orbital pain.[20] Other non-specific features include anorexia, nausea, vomiting, diarrhoea, cough, and sore throat. In epidemics fever, a flushed face, conjunctival injection, and generalised lymphadenopathy were common. A maculopapula or pale roseolar rash was reported in about half the patients and was more common in children. In one outbreak, a fifth of patients had hepatomegaly, and 10% had splenomegaly.[21] Myocarditis, pancreatitis, and hepatitis have also been described occasionally in severe infections.

Figure 3 shows the clinical course of West Nile encephalitis. Patients with neurological disease typically have a febrile prodrome of 1-7 days, which may be biphasic, before they develop neurological symptoms. Although in most cases the prodrome is non-specific, 15-20% of patients may have features suggestive of West Nile fever, including eye pain, facial congestion, or a rash, though less than 5% have lymphadenopathy.[22]

Neurological manifestations of infection are similar to those of other flaviviruses and depend on which part of the nervous system is damaged—the meninges (to give meningitis), the brain parenchyma (encephalitis), or the spinal cord (myelitis).[20] In recent outbreaks about two thirds of patients admitted to hospital had encephalitis (with or without signs of meningeal irritation), while one third had meningitis.[2 3 23] Severe generalised muscle weakness was common feature in the New York outbreak in 1999 and in subsequent outbreaks in the United States.[23] In some patients this affects only the limbs, but in others respiratory and bulbar musculature are affected and patients require ventilation. Although initially ascribed to Guillain-Barré syndrome, in most cases the weakness was probably due to anterior horn cell damage (myelitis),[20] as is seen in other flavivirus infections. During 2002, fully conscious patients with a polio-like flaccid paralysis were also recognised.[24]

Although convulsions occurred in about 30% of patients in the early descriptions of West Nile encephalitis, they did not seem to be an important feature in the outbreaks in Romania or New York.[23] Other neurological features include cranial neuropathies, optic neuritis, and ataxia. Stiffness, rigidity spasms, and tremors associated with basal ganglia damage, similar to that seen in Japanese encephalitis,[25] have also recently been recognised in West Nile encephalitis.[26]

Prognostic indicators and outcome

Overall death rates for patients admitted to hospital during recent outbreaks ranged from 4-14% but were higher in older patients.[2 23] Other risk factors were the presence of profound weakness, deep coma, failure to produce IgM antibody, immunosuppressive treatment, and coexisting illness such as hypertension and diabetes mellitus.[23 27] Neurological sequelae are common among survivors. In one study, half of patients admitted to hospital still had a functional deficit at discharge,[28] and only one third had recovered fully after one year.

Investigations

About half of patients have peripheral leukocytosis, and 15% have leucopenia.[23 28] Hyponatraemia some-

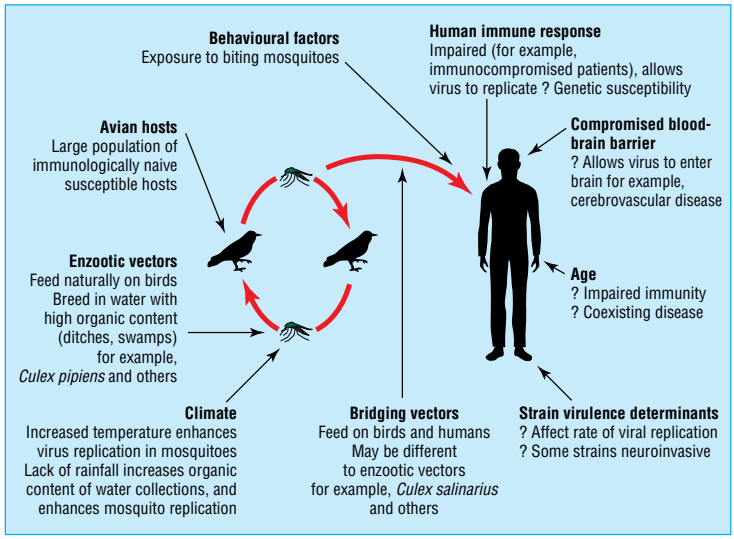

Fig 2 Factors known or postulated to be involved in the enzootic cycle of West Nile virus and epidemics of human disease

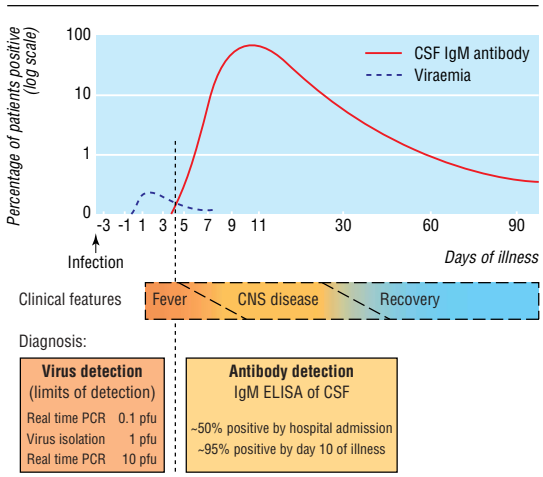

Fig 3 Clinical course of West Nile encephalitis: viraemia, development of antibody, implications for diagnosis. Limits of virus detection are expressed as plaque forming units (pfu)/100 µl; human viraemia is thought to be <10 pfu/100 µl. First day of fever is taken as first day of illness; most patients are not admitted to hospital until day 3-5 of illness

times occurs in those with encephalitis. Examination of the cerebrospinal fluid typically shows a moderate lymphocytic pleocytosis, though sometimes there may be no cells or neutrophils may predominate. Protein concentrations are moderately increased, and the glucose ratio is typically normal. Computed tomography of the brain usually yields normal results. Initial magnetic resonance imaging reports were of non-specific enhancement of the meninges or periventricular areas.[23 29] More recent studies suggest that high signal intensities on T2 weighted images in the thalamus and other basal ganglia may be an early indicator that a patient has West Nile encephalitis.[26] Nerve conduction studies typically show the reduced motor axonal amplitudes consistent with anterior horn cell damage, though there may also be some slowing of conduction velocities and some changes to sensory nerves.[20]

Diagnosis

Infection with West Nile virus is confirmed by detecting the virus or antibodies against the virus. Attempts at virus isolation from serum or cerebrospinal fluid are usually unsuccessful because viraemias are low and the virus has cleared by the time most patients present (fig 3). Newer techniques include detection of viral antigen by enzyme linked immunosorbant assay (ELISA) or of viral nucleic acid with reverse transcriptase polymerase chain reaction (PCR) or kinetic quantitative ("real time") PCR. Real time PCR, the most sensitive of these techniques, detects infection in only 55% of patients.[30] The accepted standard for rapidly diagnosing infection is therefore the detection of IgM antibodies against the virus in cerebrospinal fluid or serum, or both, by using IgM ELISAs.[31] Whereas antibody is detected in the serum of those with West Nile fever, or even asymptomatic infection, IgM in the cerebrospinal fluid is specific for infection in the nervous system. About half of patients have antibody on admission, and almost all have antibody by the seventh day of admission. A few patients, particularly those who are immunocompromised, may never make antibody, but such patients are more likely to have virus detected by isolation or PCR.

Treatment

There is no established antiviral treatment for West Nile encephalitis, or indeed any flavivirus infection. Various compounds have shown promise in vitro or in animal models. Interferon alpha has antiviral activity against West Nile virus and other flaviviruses in vitro,[32] and open clinical trials in patients with St Louis encephalitis and Japanese encephalitis have produced promising results.[33] This prompted many physicians to give the drug on a presumptive basis during the US outbreak in 2002. An open randomised trial of interferon versus placebo has been set up in the United States, though a double blind trial showed it was not effective in Japanese encephalitis.[34] High dose ribavirin is also effective in vitro and was given to patients during the Israeli outbreak in 2000, thought with no obvious benefit.[2] Immunoglobulin from patients previously infected with West Nile virus has also been given to a small number of patients with apparently promising results and is being considered for further clinical trials. Supportive treatment for patients with West Nile encephalitis includes attention to the complications of infection such as respiratory paralysis, pneumonia, pressure sores, and seizures, usually in an intensive care setting.

Prevention and control

In areas where the virus is circulating, individuals are encouraged to protect themselves from mosquito bites by wearing appropriate clothing, applying mosquito repellent containing 10-30% DEET (N,N-diethyl-3-methylbenzamide) to clothes and exposed skin, and minimising time spent outdoors during the early morning and evening, when *Culex* mosquitoes bite. This is particularly important for those in "at risk" groups, such as elderly and immunocompromised people. Measures to reduce the number of circulating mosquitoes include removing mosquito breeding sites from around the house (for example, collections of stagnant water), draining swampy areas, and applying larvicide to potential breeding sites. During outbreaks, public health authorities have sprayed with pyrethroid

Box 3: Implications for United Kingdom

- Could West Nile virus be introduced and become established in the UK? Which migrating birds might introduce the virus, and which vectors might be important in its maintenance?
- Would patients with West Nile virus be recognised, among the many patients with undiagnosed viral encephalitis?
- Does the United Kingdom have adequate infrastructure and expertise for detecting and controlling arthropod-borne infections?

Additional educational resources

- Mackenzie JS, Barrett AD, Deubel V, eds. *Current topics in microbiology and immunology: Japanese encephalitis and West Nile virus infections.* Berlin: Springer-Verlag, 2002
- Beeching N, Gill G, eds. *Lecture notes on tropical medicine.* Oxford: Blackwell Science, 2003 (in press). Useful summaries of arboviral encephalitis
- http://www.cdc.gov/ncidod/dvbid/westnile/ West Nile virus homepage of the Centres for Disease Control and Prevention, USA. Includes information for patients.

Information for patients

Encephalitis support group (www.esg.org.uk/)
This British charity is aimed at "improving the quality of life of all people affected directly and indirectly by encephalitis." It gives useful information on many aspects of encephalitis, including handout for patients on West Nile encephalitis

formulations to kill adult mosquitoes. In the United States prompt reporting of suspected cases is encouraged, and there has been intensive surveillance of mosquitoes, dead birds, horses, and sentinel chickens (chickens deliberately exposed and tested regularly for evidence of infection). There is no human vaccine for West Nile virus yet, though a crude formalin inactivated vaccine has been developed for horses, and vaccines for humans are being developed. Ultimately these may be used to protect humans at risk during epidemics, but because of its natural bird-mosquito cycle, West Nile virus will never be eradicated. Active surveillance and early mosquito control measures may offer the best hope for disease control in the future.

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1 Briese T, Jia X-Y, Huang C, Grady LJ, Lipkin WI. Indentification of a Kunjin/West Nile-like flavivirus in brains of patients with New York encephalitis. *Lancet* 1999;354:1261-62.
2 Chowers MY, Lang R, Nassar F, Ben-David D, Giladi M, Rubenshtein E, et al. Clinical characteristics of the West Nile fever outbreak, Israel, 2000. *Emerg Infect Dis* 2001;7:675-8.
3 Tsai TF, Popovici F, Carnescu C, Campbell GL, Nedlelcu NI. West Nile encephalitis epidemic in Southeastern Romania. *Lancet* 1998;352:767-71.
4 Platonov AE, Shipulin GA, Shipulina OY, Tyutyunnik EN, Rolochkina TI, Lanciotti RS, et al. Outbreak of West Nile virus infection, Volgograd Region, Russia, 1999. *Emerg Infect Dis* 2001;7:128-32.
5 Meikle J. Scientists fear deadly virus has arrived in UK. *Guardian* 2002 Oct 28.
6 Solomon T, Cardosa MJ. Emerging arboviral encephalitis. *BMJ* 2000; 321:1484-5.
7 Solomon T, Dung NM, Kneen R, Gainsborough M, Vaughn DW, Khanh VT. Japanese encephalitis. *J Neurol Neurosurg Psychiatry* 2000;68:405-15.
8 Shlim DR, Solomon T. Japanese encephalitis vaccine for travelers: exploring the limits of risk. *Clin Infect Dis* 2002;35:183-8.
9 Wasay M, Diaz-Arrastia R, Suss RA, Kojan S, Haq A, Burns D, et al. St Louis encephalitis: a review of 11 cases in a 1995 Dallas, Tex, epidemic. *Arch Neurol* 2000;57:114-8.
10 Mackenzie JS, Broom AK, Hall RA, Johansen CA, Lindsay MD, Phillips DA, et al. Arboviruses in the Australian region, 1990 to 1998. *Commun Dis Intell* 1998;22:93-100.
11 McIntosh BM, Jupp PG, Dos Santos I, Meenehan GM. Epidemics of West Nile and Sindbis viruses in South Africa with Culex (culex) univittatus Theobold as vector. *S Afr J Sci* 1976;72:295-300.
12 Spigland I, Jasinska-Klingberg W, Hofsbi E, Goldblum N. Clinical and laboratory observations in an outbreak of West Nile fever in Israel. *Harefua* 1958;54:275-81.
13 Mostashari F, Bunning ML, Kitsutani PT, Singer DA, Nash D, Cooper MJ, et al. Epidemic West Nile encephalitis, New York, 1999: results of a household-based seroepidemiological survey. *Lancet* 2001;358:261-4.
14 Gould EA, Zanotto PM, Holmes EC. The genetic evolution of flaviviruses. In: Saluzzo JF, Dodet B, eds. *Factors in the emergence of arbovirus diseases.* Paris: Elselvier, 1997:51-63.
15 Beasley DW, Li L, Suderman MT, Barrett AD. Mouse neuroinvasive phenotype of West Nile virus strains varies depending upon virus genotype. *Virology* 2002;296:17-23.
16 Rappole JH, Derrickson SR, Hubalek Z. Migratory birds and spread of West Nile virus in the Western Hemisphere. *Emerg Infect Dis* 2000;6:319-28.
17 Lanciotti RS, Roehrig JT, Deubel V, Smith J, Parker M, Steele K, et al. Origin of the West Nile virus responsible for an outbreak of encephalitis in the northeastern United States. *Science* 1999;286:2333-7.
18 West Nile virus activity—United States, October 10-16, 2002, and update on West Nile virus infections in recipients of blood transfusions. *MMWR Morb Mortal Wkly Rep* 2002;51:929-31.
19 Taylor R, Work TH, Harlbut HS, Rizk F. A study of the ecology of West Nile virus in Egypt. *Am J Trop Med Hyg* 1956;5:579-620.
20 Solomon T, Vaughn DW. Clinical features and pathophysiology of Japanese encephalitis and West Nile virus infections. In: Mackenzie JS, Barrett AD, Deubel V, eds. *Current topics in microbiology and immunology: Japanese encephalitis and West Nile virus infections.* Berlin: Springer-Verlag, 2002:171-94.
21 Goldblum N, Sterk VV, Paderski B. West Nile fever: the clinical features of the disease and the isolation of West Nile virus from the blood of nine human cases. *Am J Hyg* 1954;59:89-103.
22 Asnis DS, Conetta R, Teixeira AA, Waldman G, Sampson BA. The West Nile virus outbreak of 1999 in New York: the Flushing Hospital experience. *Clin Infect Dis* 2000;30:413-8.
23 Nash D, Mostashari F, Fine A, Miller J, O'Leary D, Murray K, et al. The outbreak of West Nile virus infection in the New York City area in 1999. *N Engl J Med* 2001;344:1807-14.
24 Leis AA, Stokic DS, Polk JL, Dostrow V, Winkelmann M. A poliomyelitis-like syndrome from West Nile virus infection. *N Engl J Med* 2002;347:1279-80.
25 Misra UK, Kalita J. Movement disorders in Japanese encephalitis. *J Neurol* 1997;244:299-303.
26 Solomon T, Fisher AF, Beasley DWC, Mandava P, Granwchr BP, Langsjoen H, et al. Natural and nosocomial infection in a patient with West Nile fever. *Clin Infect Dis* (in press).
27 Cernescu C, Ruta SM, Tardei G, Grancea C, Moldoveanu L, Spulbar E, et al. A high number of severe neurologic clinical forms during an epidemic of West Nile virus infection. *Rom J Virol* 1997;48:13-25.
28 Weiss D, Carr D, Kellachan J, Tan G, Phillips M, Bresnitz E, et al. Clinical findings of West Nile virus infection in hospitalized patients, New York and New Jersey, 2000. *Emerg Infect Dis* 2001;7:654-8.
29 Petersen LR, Marfin AA. West Nile virus: a primer for the clinician. *Ann Intern Med* 2002;137:173-9.
30 Lanciotti RS, Kerst AJ, Nasci RS, Godsey MS, Mitchell CJ, Savage HM, et al. Rapid detection of West Nile virus from human clinical specimens, field-collected mosquitoes, and avian samples by a TaqMan reverse transcriptase-PCR assay. *J Clin Microbiol* 2000;38:4066-71.
31 Martin DA, Biggerstaff BJ, Allen B, Johnson AJ, Lanciotti RS, Roehrig JT. Use of immunoglobulin m cross-reactions in differential diagnosis of human flaviviral encephalitis infections in the United States. *Clin Diagn Lab Immunol* 2002;9:544-9.
32 Anderson JF, Rahal JJ. Efficacy of interferon alpha-2b and ribavirin against West Nile virus in vitro. *Emerg Infect Dis* 2002;8:107-8.
33 Rahal J, Anderson J, Rosenberg C, Reagan T, Thompson L. Effect of interferon alpha-2b on St. Louis (SL) virus meningoencephalitis: clinical and laboratory results. Infectious Diseases Society of America, 40th Meeting 2002, Chicago, Il:A823.
34 Solomon T, Dung NM, Wills B, et al. A double-blind placebo-controlled trial of interferon alpha in Japanese encephalitis. *Lancet* 2003;361:821-6.

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Endpiece

Confide in your doctor

If there is a reason to help a stranger and poor man, then offer your services to him enthusiastically, because love to people goes together with love of science. The sick patients who are afraid of their illness and confide in the humane feelings of the doctor often become well.

Hippocrates

Dimitrios Kassimos, Birmingham